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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, DEEPAK R	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 06/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,505	CARTER ET AL.	
	Examiner	Art Unit	
	Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,11-13,15-22,24,25,27-29,31,32,34 and 35* is/are rejected.

7)☐ Claim(s) *2,5-10,14,23,26,30 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 27, 2004 has been entered.

Claims 1-2 and 4-35 are pending in this application.

Election/Restrictions

Applicant's elected the species of Example 59 (page 270, Table 1) in paper no. 8. The prior art rejection of the previous office action has been overcome by applicant's amendments and as per the guidelines of MPEP § 803.02, the search and examination is expanded to compounds of formula (I) wherein the aryl groups of R^1 and R^2 are joined by acyclic groups (i.e., R^1, R^2, X and Z are as defined in the claims and **none** of the terms $-(CR^6R^7)-$, $-(CR^8R^9)-$ and $-(CR^{10}R^{11})-$ together form a cyclic group), and art was found. The previously withdrawn claims 11-13 are rejoined and examined to the extent readable on the above subgenus, i.e., the compounds of formula (I) wherein the two aryl groups are joined by acyclic linking groups.

The generic subject matter wherein the terms $-(CR^6R^7)-$, $-(CR^8R^9)-$ and $-(CR^{10}R^{11})-$ together form a cyclic group from the claims is withdrawn from further consideration, pursuant to 37 CFR 1.142(b) as being drawn to nonelected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-22, 24-25, 27-29, 31-32 and 34-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of rheumatoid arthritis, osteoarthritis, fever, and asthma, does not reasonably provide enablement for a method for modulation of chemokine or chemokine receptor activity; a method for treating various diseases such as Crohn's disease, inflammatory diseases, multiple sclerosis, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

Claims 16-18, 28 and 35 recite "a method for modulation of chemokine receptor activity" and the specification page 289, lines 11-13 provides that the term "Modulation" encompasses antagonism, partial antagonism and partial agonism. However, the compounds were not shown

to have all these properties. The specification only provides test data related to measuring antagonism of MCP-1 and there is no disclosure, how one of ordinary skill in the art can extrapolate this data to find the 'chemokine modulation' activity of the compounds. For example, it is revolutionary for a compound to be effective as an antagonist and partial agonist/antagonist. The specification did not provide any competent tests or data to establish that the compounds have the claimed 'chemokine receptor modulating activity'. Havlioglu et al. (Journal of Neurovirology 2002) provide that "Chemokines are classified into several families according to their structural features" (page 486); "Although some viral-derived chemokine inhibitors have been reported, very little is known about endogenously produced chemokine inhibitors" (page 487); and conclude that "The studies on the interplay between chemokine pathways and other signal transduction pathways are only at the beginning. Mechanisms underlying the complex regulation of chemokine signaling inside and outside the nervous system await further investigation with combined molecular, biochemical and functional approaches" (page 489). This establishes the uncertainties and the level of unpredictability in the relevant state of the art and therefore, one of ordinary skill in the art would be required to go through undue experimentation to find the modulating activity of the compounds.

The instant claims recites method of treatment of various disorders and the specification fails to enable one skilled in the art for the recited use. The use disclosed in the specification is as therapeutic agents for the treatment of diseases listed in pages 289-290, which includes various inflammatory diseases, etc. First, the claims cover 'disorders' having diverse mechanisms and/or involving various organs and parts of a human body and therefore, the treatment recited in the claims is extremely broad. Further, there is no description regarding how

to identify the subject 'in need of such treatment' of these assorted diseases. Test procedures for measuring the activity of the compounds in terms of antagonism of MCP-1 is provided on pages 285-287, however, there is nothing in the disclosure regarding how this *in vitro* assay correlates to the treatment of the disorders of the instant claims. The data provided in insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the compounds. The area of receptor interactions is highly structure specific and unpredictable. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of the treatment is identified and further, how all types of disorders of the claims having diverse etiologies are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the inhibitory data provided is insufficient for one of ordinary skill in the art in order to extrapolate to all types of disorders of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims.

Enablement for the scope of "treatment of inflammatory disorders" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place individually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all,

or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name, given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neurophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus.

Hence, these types of inflammations are treated with antibiotics. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammatory disorders. It establishes that it is not reasonable to any agent to be able to treat inflammatory disorders generally.

The therapeutic method of the instant claims includes treatment of inflammatory bowel disease, e.g., Crohn's disease, ulcerative colitis, psoriasis, etc. which have been proven very difficult to treat because 'there is no known cause' (see The Merck Manual online edition). Bremner et al. (Expert Opin. Pharmacother. 2002) provide that "New therapies that affect immunomodulation offer the possibility of disease control in those unresponsive to conventional therapy and may reduce the need for further surgery. However, these treatments remain to be fully evaluated" (see page 820). Singh et al. (British Journal of Surgery, 2001) provide that 'the etiology and pathogenesis of inflammatory bowel diseases are incompletely understood' (see page 1558). Robinson (Eur. J. Surg. 1998) indicates that "Despite the growing list of medications and formulations prompted for the treatment of IBD, no single drug or recognized combination has yet been confirmed as dependably clinically effective"; "All physicians who care for UC and CD patients enthusiastically await more optimal regimens for these challenging disorders" (see page 90). This state of the art analysis indicative of the unpredictability related to the treatment of inflammatory bowel diseases.

Further, the list of the diseases includes multiple sclerosis, which has traditionally been very difficult or impossible to treat effectively with chemotherapeutic agents. See e.g., Casanova

et al. (PubMed Abstract enclosed) state that "Multiple Sclerosis (MS) is a disorder in which the pathogenesis is not clearly understood", see the abstract.

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating or lessening the severity' effect of a 'disease' solely based on the inhibitory activity disclosed for the compounds.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the

unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. Claim 4 depends from canceled claim 3.
2. In claim 12, the recitations "R^{14} and R^{14a} are H; R^{15} is H; n is 1" (page 51, lines 26-30) are redundant because claim 1 (on which claim 12 is dependent) recites exactly the same definitions for each of these variables.
3. Claim 13 recites the limitation "alternatively, R^3 and R^{12} join to form cyclopropyl, cyclopentyl or cyclohexyl" in page 53, lines 16-17. There is insufficient antecedent basis for this limitation in claim 1 on which claim 13 is dependent (via claims 12 and 11).
4. Claim 13 recites the limitation " X is $CHR^{16}R^{17}$ " in line 2. There is insufficient antecedent basis for this limitation in claim 1 on which claim 13 is dependent (via claims 12 and 11). Claim 1 does not define X to be the above moiety, it may have been a typographical error for -- -$CHR^{16}\underline{N}R^{17}$- --.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 11, 12 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Antoku et al., EP 443862. The reference teaches triamine compounds, see formula (I) in page 1, and the specific compound disclosed as Reference Example 1 (page 21). The reference compounds are taught to be useful as medicinal agents, see the abstract. The instant claims require that R^3 and R^6 can not be H at the same time and therefore, if R^3 is H, R^6 must be other than H, and the definition of R6 includes alkyl, e.g., methyl, etc. Therefore, the instantly claimed compounds differ from the reference compounds by a $-CH_2$ group and it is well established that compounds that differ by a $-CH_2$ group are structural homologs. It would have been obvious to one having ordinary skill in the art at the time of the invention to modify the reference compounds to prepare the structural homolog. One having ordinary skill in the art would have

been motivated to prepare the instantly claimed compounds because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are *prima facie* obvious, absent a showing of unexpected results. *In re Hass*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

Allowable Subject Matter

Claims 2, 5-10, 14, 23, 26, 30 and 33 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form **to the extent of the examined subgenus indicated above** (i.e., compounds of formula (I) wherein the two aryl groups are joined by acyclic linking groups), including all of the limitations of the base claim and any intervening claims.

Claim 13 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr.

Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

June 17, 2004